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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/707,747	01/08/2004	John H Paul	1372.120.PRC	1746

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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/707,747	PAUL ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8 January 2004*. 4/14/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 refers to a unique gene sequence as an 87-base-pair region when amplified by RT-PCR, yet in claim 3, this region is a 91-base-pair region. Clarification is required.

Claim 15 refers to a unique gene sequence as a 91-base-pair region when amplified by nucleic acid sequence-based amplification, yet in claim 10, this region is a 87-base-pair region. In addition, it is claimed that nucleic acid sequence-based amplification is used to amplify this region using SEQ ID. Nos 4, 5 and 6 (claims 11-13), yet it is also claimed in claim 15 that RT-polymerase chain reaction is used, which is inconsistent with earlier claims, since RT-polymerase chain reaction is used with SEQ ID Nos. 1-3 in claims 4-6. Clarification is required. For the purposes of examination, Claim 15 will be interpreted as referring to nucleic acid sequence-based amplification.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al., (Appl. Environ. Microbiol. (2000) 66: 4641-4648).

With regard to claims 1, 7, and 8, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample comprising the steps of: identifying a unique gene sequence associated with the organism *K. brevis* (Figure 1A and B and p. 11726, column 1, lines 8-14); amplifying the unique gene sequence contained in the water sample using at least one purified primer (p. 11725, column 1, lines 13-24 and Table 2, supporting information); and detecting the presence of the unique gene sequence within the sample (by sequencing PCR products, p. 11725, column 1, lines 25-30).

With regard to claim 2, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the amplification step is performed by reverse transcriptase polymerase chain reaction (p. 11725, column 1, lines 17-24).

With regard to claim 3, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the unique gene sequence is a 91-base-pair region of the *K. brevis* rbcL gene (p. 11724, column 2, lines 29-32 and Table 1, supporting information).

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using a real-time reverse transcriptase polymerase chain reaction with a fluorogenically-labeled internal probe and epifluoresence microscopy.

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using a real-time reverse transcriptase polymerase chain reaction with a fluorogenically-labeled internal probe and epifluoresence microscopy.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23), internal probes labeled with a fluorogenic compound (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14), and epifluorescence microscopy (using Lightcycler, p. 4643, column 1, lines 30-31 and p. 4645, column 1, lines 29-35). Bowers demonstrates specific detection of *Pfiesteria* species in the

presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Bowers since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. Furthermore, the use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing.

6. Claims 4-6, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al., (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of

Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claim 4, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the purified primer sequence for reverse transcriptase polymerase chain reaction is SEQ ID NO: 1 (Table 1, supporting information, GenBank Accession No. AY119786, positions 729-748).

With regard to claim 5, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the purified primer sequence for reverse transcriptase polymerase chain reaction is SEQ ID NO: 2 (Table 1, supporting information, GenBank Accession No. AY119786, positions 819-798).

With regard to claim 6, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the internal probe for reverse transcriptase polymerase chain reaction is SEQ ID NO: 3 (Table 1, supporting information, GenBank Accession No. AY119786, positions 758-775).

With regard to claim 14, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, comprising the steps of: identifying a unique gene sequence associated with the organism *K. brevis,* wherein the unique gene sequence is a 87 (or 91)-base-pair region of the *K. brevis* rbcL gene (Table 1, supporting information, GenBank Accession No. AY119786); amplifying the unique gene sequence contained in the water sample using at least one purified primer

(p. 11725, column 1, lines 13-24 and Table 2, supporting information), wherein the amplification step is performed by reverse transcriptase polymerase chain reaction (p. 11725, column 1, lines 17-24), wherein the purified primer sequence is chosen from the group consisting of SEQ ID NOs: 1 and 2 (Table 1, supporting information, GenBank Accession No. AY119786, positions 729-748 and 819-798), wherein the internal probe is SEQ ID NO. 3 (Table 1, supporting information, GenBank Accession No. AY119786, positions 758-775), and detecting the presence of the unique gene sequence within the sample (by sequencing PCR products, p. 11725, column 1, lines 25-30).

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using a real-time reverse transcriptase polymerase chain reaction with a fluorogenically-labeled internal probe and epifluoresence microscopy.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23), internal probes labeled with a fluorogenic compound (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14), and epifluorescence microscopy (using Lightcycler, p. 4643, column 1, lines 30-31 and p. 4645, column 1, lines 29-35). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Bowers since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. Furthermore, the use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art

compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair

sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

7. Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al., (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of Leone et al., (Nucleic Acids Res. (1998) 26: 2150-2155).

With regard to claim 9, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, comprising the steps of: identifying a unique gene sequence associated with the organism *K. brevis* (Figure 1A and B and p. 11726, column 1, lines 8-14); amplifying the unique gene sequence contained in the water sample using at least one purified primer (p. 11725, column 1, lines 13-24 and Table 2, supporting information); and detecting the presence of the

unique gene sequence within the sample (by sequencing PCR products, p. 11725, column 1, lines 25-30).

With regard to claim 10, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the unique gene sequence is an 87-base-pair region of the *K. brevis* rbcL gene (p. 11724, column 2, lines 29-32 and Table 1, supporting information).

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using nucleic acid sequence based amplification with a labeled internal probe.

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using nucleic acid sequence based amplification with a labeled internal probe.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23) and internal probes labeled with a fluorogenic compound (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Bowers and Leone since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis* in water samples. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing.

Furthermore, because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis.*

8. Claims 11-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al., (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of Leone et al., (Nucleic Acids Res. (1998) 26: 2150-2155) and further in view of Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claim 11, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the purified primer sequence is SEQ ID NO: 4 (Table 1, supporting information, GenBank Accession No. AY119786, positions 733-751).

With regard to claim 12, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the purified primer sequence is SEQ ID NO: 5 (Table 1, supporting information, GenBank Accession No. AY119786, positions 819-798, representing the 22 3' most bases of this NASBA primer complementary to the target; the remaining portion SEQ ID No. 5 serves as a transcription initiation sequence, see Leone, Figure 6).

With regard to claim 13, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, wherein the internal

probe is SEQ ID NO: 6 (Table 1, supporting information, GenBank Accession No. AY119786, positions 763-783 in this beacon probe are complementary to the target).

With regard to claim 15, Yoon teaches a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample, comprising the steps of: identifying a unique gene sequence associated with the organism *K. brevis,* wherein the unique gene sequence is a 91 (or 87)-base-pair region of the *K. brevis* rbcL gene (Table 1, supporting information, GenBank Accession No. AY119786); amplifying the unique gene sequence contained in the water sample using at least one purified primer (p. 11725, column 1, lines 13-24 and Table 2, supporting information), wherein the purified primer sequence is chosen from the group consisting of SEQ ID NOs: 4 and 5 (Table 1, supporting information, GenBank Accession No. AY119786, positions 733-751 and 819-798), wherein the internal probe is SEQ ID NO. 6 (Table 1, supporting information, GenBank Accession No. AY119786, positions 763-783), and detecting the presence of the unique gene sequence within the sample (by sequencing PCR products, p. 11725, column 1, lines 25-30).

Yoon does not teach a method of detecting the presence of at least one dinoflagellate, specifically *K. brevis,* in a water sample using nucleic acid sequence based amplification with a labeled internal probe.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23) and internal probes labeled with a fluorogenic compound (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14). Bowers

demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a *K. brevis* internal probe, the internal probe having a label attached thereto.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon, Bowers and Leone since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis* in water samples. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a

rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing.

Furthermore, because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis*.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate

compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of

extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Conclusion

9. Claims 1-15 are rejected. No claims are allowable.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas
Patent Examiner
David C. Thomas 2/24/06

JEFFREY FREDMAN
PRIMARY EXAMINER
2/24/06